1 Summary of Safety and Effectiveness Data

1.1 General Information

Device Generic Name:	Implantable system for responsive electrical stimulation of the brain
Device Trade Name:	NeuroPace® RNS® System, consisting of: NeuroPace® RNS® Neurostimulator Kit (model RNS-300M-K) Connector Cover Kit (model CC-01-K) Craniectomy Template Kit (model CT-01-K) Ferrule Kit (model F-01-K) Cranial Prosthesis Kit (model P-01-K) NeuroPace® Depth Lead Kit (models: DL-330-3.5-K, DL-330-10-K, DL-344-3.5-K, DL-344-10-K) NeuroPace® Cortical Strip Lead Kit (models: CL-315-10-K, CL-325-10-K, CL-335-10-K) NeuroPace® Lead Accessory Kit (model LA-02-K) NeuroPace® Programmer Kit (model PGM-300-K) Accessory Kit (model ACC-01-K) NeuroPace® Remote Monitor Kit (model DTR-300-K) Wand (model W-02) NeuroPace® Patient Data Management System (model 4340) Magnet (model M-01)
Applicant's Name and Address:	NeuroPace, Inc. 455 N. Bernardo Avenue Mountain View, California 94043, USA
PMA Number:	(To be completed by FDA.)
Date of Panel Recommendation:	(To be completed by FDA.)
Date of Notice of Approval to the Applicant:	(To be completed by FDA.)

1.2 Indication for Use

The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

For purposes of this document the NeuroPace® RNS® System will be referred to as the RNS® System.

1.3 Contraindications, Warnings, and Precautions

1.3.1 Contraindications

The RNS® System is contraindicated for:

- Patients at high risk for surgical complications
- Patients who have medical devices implanted that deliver electrical energy to the brain

The following medical procedures are contraindicated for patients with an implanted RNS® System. Energy from these procedures can be sent through the implanted brain stimulation system and cause permanent brain damage which may cause severe injury, coma, or death. Brain damage can occur from any of the listed procedures even if the RNS® Neurostimulator is turned off or if the Leads are not connected to the Neurostimulator, and can occur even if the Neurostimulator has been removed if any Leads or any part of a Lead remain.

- MR imaging is contraindicated for patients with an implanted RNS® System. Do not perform an MRI on a patient with any implanted RNS® Neurostimulator or Lead (or any portion of a Lead).

  The RNS® System is MR Unsafe. Testing has not been performed to define conditions of use to ensure safety of the RNS® System in an MR environment.
- Diathermy procedures are contraindicated in patients implanted with an RNS® Neurostimulator and associated Leads. (Diathermy is any treatment that uses high-frequency electromagnetic radiation, electric currents, or ultrasonic waves to produce heat in body tissues.) Patients absolutely CANNOT be treated with any type of shortwave, microwave, or therapeutic ultrasound diathermy device whether or not it is used to produce heat. These treatments should not be applied anywhere on the body
- Electroconvulsive Therapy (ECT) is contraindicated for patients with an implanted RNS® System.
- Transcranial Magnetic Stimulation (TMS) is contraindicated for patients with an implanted RNS® System.

1.3.2 Warnings and Precautions

Please refer to the device labeling for warnings and precautions.

1.4 Device Description

The NeuroPace® RNS® System includes a cranially implantable programmable RNS® Neurostimulator that senses and records brain electrical activity. In response to the detection of previously identified patterns the Neurostimulator is designed to deliver responsive electrical stimulation to the brain to interrupt those patterns before the patient experiences clinical seizures. The implantable device consists of a responsive Neurostimulator and one or two Leads that connect to the Neurostimulator.

A description of each of the RNS® System components follows.

NeuroPace® RNS® Neurostimulator Kit (model RNS-300M-K)

The RNS® Neurostimulator contains electronic circuitry and a battery that are hermetically sealed within a flat curved titanium enclosure. The Neurostimulator is implanted and contained within the cranium coplanar with the skull surface and is covered by the scalp. A Ferrule provides a means to mechanically support and secure the Neurostimulator in the skull so that there is no direct contact with the

brain. The Neurostimulator is connected to one or two Leads that are surgically placed in or near the epileptic seizure foci in the brain. The Neurostimulator monitors electrocorticographic (ECoG) activity and can be programmed to detect abnormal electrical activity such as epileptiform patterns. When detection criteria are met, the Neurostimulator delivers short trains of constant current, charge balanced pulses (responsive stimulation) to one or two epileptic foci. Detection and stimulation parameters can be non-invasively adjusted to optimize control of clinical epileptic seizures for each patient.

NeuroPace® Leads

The NeuroPace® Leads provide an interface through which electrical activity of the brain can be sensed and recorded by the RNS® Neurostimulator and through which responsive electrical stimulation can be delivered. Depth Leads are stereotactically introduced into epileptic foci in the brain and Cortical Strip Leads are placed on the surface of the brain near epileptic foci. The Leads have a flexible, silicone Lead body 1.27 mm in diameter that encloses four insulated wires, and have four platinum/iridium electrodes at their distal end. The proximal end (identical for both the Depth and Cortical Strip Leads) has four contacts designed to connect to the RNS® Neurostimulator.

The NeuroPace® Depth Leads (models: DL-330-3.5-K, DL-330-10-K, DL-344-3.5-K, DL-344-10-K) have four cylindrical electrodes at their distal end that deliver stimulation to the target site. These Leads are provided in two lengths (30 cm and 44 cm). Two models of each length are provided; each is defined by the center to center distance of the distal electrodes (3.5 mm spacing and 10 mm spacing).

The NeuroPace® Cortical Strip Leads (models: CL-315-10-K, CL-325-10-K, CL-335-10-K) have a flat electrode strip (0.3 by 1.6 inches) having a single row of four disk-shaped electrodes at the distal end that deliver stimulation to the target area. These Leads are provided in three lengths (15 cm, 25 cm and 35 cm). One model of each length with center-to-center spacing of 10 mm is provided.

NeuroPace® Programmer Kit (model PGM-300-K)

The NeuroPace® Programmer utilizes a Wand containing the circuitry to communicate with an RNS® Neurostimulator. The Programmer provides the clinician with a user interface to select and download operating parameters to the RNS® Neurostimulator for detection and responsive stimulation settings, to view real-time ECoG signals, to test the RNS® System integrity, and to upload data and diagnostic information from the RNS® Neurostimulator for viewing. The Programmer may be used on its own to review previously retrieved Neurostimulator information, perform detection analysis and communicate using the Internet by way of a secure connection with the NeuroPace® Patient Data Management System (PDMS) to upload information previously uploaded from the Neurostimulator.

NeuroPace® Remote Monitor Kit (model DTR-300-K)

The NeuroPace® Remote Monitor is a home-use monitoring device that utilizes a Wand to communicate with an implanted RNS® Neurostimulator. The Remote Monitor is similar to the Programmer; however, the Remote Monitor cannot be

used to change operating parameters of the Neurostimulator. It is provided to a patient or caregiver to collect data from the implanted RNS® Neurostimulator and to upload these data using telephone lines or the Internet by way of a secure connection to the PDMS. The uploaded data are accessible for review by physicians through the PDMS web site using a secure web browser. This offers a convenient option for remotely monitoring the RNS® Neurostimulator implanted in a patient between clinic visits.

NeuroPace® Patient Data Management System (model 4340)

The NeuroPace® Patient Data Management System (PDMS) is used for storage and access to historical Neurostimulator and patient data. During synchronization of the Programmer or Remote Monitor with the PDMS, Neurostimulator information regarding detections and stimulations, as well as stored ECoG recordings and Neurostimulator self-diagnostic information are uploaded automatically to the PDMS and combined with previously uploaded information. Reports can be accessed and reviewed by authorized users on the PDMS on the Internet (available through www.neuropace.com). This central database allows the physician to assess the patient's response over time and to assist the physician in optimal detection and stimulation programming. Data transferred using the PDMS are encrypted to ensure security and integrity of the data.

Magnet (model M-01)

While the Magnet (90 Gauss) is held in place over the implanted RNS® Neurostimulator, stimulation therapy is withheld. Stimulation therapy is enabled again upon removal of the Magnet. Detection and ECoG storage continue while the Magnet is in place. Swiping the Magnet over the Neurostimulator will trigger the Neurostimulator to store a record of the date and time of the magnet swipe. The Neurostimulator may also be programmed by the physician so that a Magnet swipe triggers ECoG storage.

1.5 Alternative Practices and Procedures

There are currently three alternative modalities available for the treatment of epilepsy: antiepileptic drugs, vagus nerve stimulation, and resective epilepsy surgery. Antiepileptic medications are tried first, usually in monotherapy. If the first antiepileptic medication is not effective, alternative antiepileptic medications are tried alone or in polytherapy. In the 30-40% of people with epilepsy for whom medications are not effective or who have unacceptable medication related side effects, vagus nerve stimulation or resective neurosurgery may be an option. Vagus nerve stimulation therapy is adjunctive to antiepileptic drug therapy. Neurosurgery for the treatment of epilepsy usually requires removal of some portion of the brain; therefore seizure onset must be localized to a well defined region of brain that can be resected without incurring unacceptable neurological deficits.

Stimulation of the brain has been proposed as a nondestructive and reversible therapy for epilepsy. The RNS® System is designed to record brain electrical activity and to deliver stimulation directly to the seizure focus when abnormal electrocorticographic patterns (as defined by the physician) occur.

1.6 Marketing History

The RNS® System has not been marketed in the United States or any other country.

1.7 Potential Adverse Effects of the Device on Health

The RNS® Neurostimulator and NeuroPace Leads were implanted in 256 participants in three clinical investigations. As of May 12, 2011, there were 903 patient years of implant experience and 819 years of stimulation experience. The average length of post-implant participation in the RNS® System Feasibility, Pivotal and Long-term Treatment (LTT) Clinical Investigations was 3.3 years (range 5 weeks to 7 years).

1.7.1 Observed Adverse Events

Adverse event data are collected from all subjects implanted with the RNS® Neurostimulator and Leads while participating in any RNS® System study.

Adverse Events During the Blinded Evaluation Period (Pivotal Study)

Adverse events (**Table 1-4**) reported in ≥ 2.5% of subjects (3 subjects or more) in the Treatment group were contusion due to seizure (7.3%), nasopharyngitis (6.3%), skin laceration due to seizure-related trauma (6.3%), depression (5.2%), headache (5.2%), increased complex partial seizures (4.2%), influenza (4.2%), pain of skin (4.2%), abdominal pain (3.1%), adverse drug reaction (3.1%), and vomiting (3.1%). In the Sham stimulation group, adverse events reported in ≥ 2.5% of subjects were nasopharyngitis (8.6%), headache (7.5%), dysaesthesia (5.4%), therapeutic agent toxicity (usually anticonvulsant side effects, 5.4%), upper respiratory tract infection (4.3%) balance disorder (3.2%), increased complex partial seizures (3.2%), head injury (3.2%), influenza (3.2%), pharyngitis (3.2%), skin laceration due to seizure-related trauma (3.2%), and vomiting (3.2%).

Device-Related Serious Adverse Events Implant Through Two Years (Pivotal Study)

Over the RNS® System Pivotal study with 379 patient years of implant experience and over 328 patient years of stimulation experience, there were no serious unanticipated device-related adverse events. Over the entire two years of post-implant follow-up, device-related (or device relation uncertain) serious adverse events that occurred in more than 2 of the 191 subjects were implant site infection (3.7%), increased complex partial seizures (3.1%), device lead damage (2.6%), increased tonic-clonic seizures (2.6%), and device lead revision (2.1%). See **Table 1-5** for a summary of all device-related adverse events during the Pivotal Study.

Device-Related Serious Adverse Events (Combined RNS® System Studies)

Over the entire RNS® Studies experience with over 903 patient years of implant experience and 819 patient years of stimulation experience, there were no serious unanticipated device-related adverse events. No single device-related

serious adverse event affected more than 5.9% of subjects (**Table 1-6**). Device-related (or device relation uncertain) serious adverse events that occurred in ≥ 2.5% of the 256 subjects at any time post-implant were implant site infection (5.9%), premature battery depletion (4.3%), increased tonic-clonic seizures (3.9%), medical device removal (3.5%), increased complex partial seizures (3.1%), and device lead damage (2.7%).

Subject Deaths

There were 11 subject deaths in the RNS® System trials as of October 24, 2012. Two of the deaths were by suicide; both subjects had a prior history of depression, and one did not have responsive stimulation enabled. One death occurred due to status epilepticus in a subject who had subtherapeutic levels of antiepileptic medications. Another death was due to lymphoma. Seven deaths were attributed to Sudden Unexplained Death in Epilepsy (SUDEP); 4 were considered definite SUDEP, 1 as probable SUDEP, and 2 were considered possible SUDEP; 2 of the 7 subjects did not have responsive stimulation enabled at the time of death. The rate of SUDEP for subjects whose Neurostimulators were programmed to provide responsive stimulation is 4.5 SUDEP events per 1000 patient years of stimulation, consistent with the comparator rate of 9.3 SUDEP events per 1000 patient years, which is assumed to be the background SUDEP rate for this subject population. Based on the experience to date, the risk of SUDEP is not increased in subjects receiving responsive stimulation with the RNS® System.

1.7.2 Potential Adverse Events

Possible complications of the RNS® System include those related to the implantation procedure, those related to performance of the Neurostimulator and Leads and those related to long-term patient tolerance of the implant. Adverse events which may potentially occur, but were not reported in the clinical trials for the RNS® System, include:

Allergic reaction to the implanted material
Lead migration
Stroke
Brain abscess

1.8 Summary of Preclinical Studies

The following is a summary of the preclinical testing performed to assure conformance to design specifications of the RNS® System. Verification and validation were conducted to provide sufficient data to support the intended use of the RNS® System. Verification tests and validation activities were performed successfully and met their acceptance criteria.

1.8.1 Laboratory Studies

1.8.1.1 Risk Analysis

The RNS® System was developed in accordance with design controls and a risk management process that conformed with ISO 14971:2000 to identify and

manage RNS® System hazards and risks and to eliminate risk or reduce it to as low as reasonably practicable given the intended use.

1.8.1.2 Product Testing

The RNS® Neurostimulator products, components, accessories and surgical tools passed verification testing.

Mechanical and Electrical Verification

- Battery: The battery was subjected to a series of performance testing including battery capacity verification (longevity) using multiple discharge rates, forced and rapid discharge testing, and environmental testing per UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria (UNDOT), 4th revised edition, section 38.3 (Lithium batteries).
- Feedthrough: The feedthrough utilized in the RNS® Neurostimulator underwent safety, environmental, physical and electrical verification testing, including hermeticity (helium leak test) per Mil Std 202, Method 112.
- Integrated Circuits: Components underwent electrical test after accelerated life test exposure (per Mil Std 883, Method 1005).

Additional testing of the RNS® Neurostimulator included:

- Sensing capability
- Measurements, detection, and memory electrical verification
- Current output amplitude, pulse width, and other timing parameters per ISO 14708-1:2000, Sec. 16 (modified requirement limit is stricter than standard)
- Current leakage and charge balanced pulses
- Battery Life and Neurostimulator End of Service (EOS)
- Geometry per ISO 14708-1:2000, Sec. 15.2
- Ferrule compatibility
- Wet rub test per ISO 14708-1:2000, Sec. 13.1
- Mechanical shock per ASTM D 3332-99
- Mechanical vibration per ISO 14708-1:1997 (lower frequency limit changed from 5 Hz to 10 Hz); CEI/IEC 60068-2-47
- Atmospheric pressure changes per ISO 14708-1:1997
- Shipping and storage temperature cycles per ISO 14708-1:2000 26.2; IEC 60601-1; IEC 68-2-14, test Nb
- Thermal shock per ASTM D 4169-99
- Temperature rise due to fault condition per ISO 14708-1:2000 Part 17
- RNS® Neurostimulator and Ferrule severe impact resistance and cranial rigidity tests
- Helium leak test for hermeticity performed during manufacturing on all devices
- Connector electrical isolation per ISO 14708-1:2000, Sec. 16.3
- Connector Plug fluid seal analysis
- Connector repeated insertion/extraction force test

- Connector lead fixation test

Software Validation

The RNS® Neurostimulator software was developed verified and validated according to IEC 62304:2006 and as per the product software requirement specification. Preclinical validation of software as part of the RNS® System was performed using simulated user scenarios.

EMC/EMI, Radio and Co-existence Verification

The RNS® Neurostimulator System EMC/EMI and wireless radio testing was performed per applicable regulations and standards including:

- EMC per ISO 14708-3:2008, Section 27; testing included mobile phone frequencies per ANSI/AAMI PC69:2000
- EMC/EMI testing per IEC 60601-1-2:2007
- Wireless radio testing per U.S. FCC CFR Title 47 Part 2 and 15

Wireless co-existence testing of the RNS® System was performed in potentially interfering use environments, such as near metal detectors, electronic article surveillance (EAS) systems, radio frequency identification (RFID) readers, operating room, and mobile phones.

The RNS® Neurostimulator, Ferrule, Leads, and Cranial Prosthesis were evaluated for radiographic (X-ray) imaging safety and compatibility per ISO 14708-1:2000, Sec. 13.3 and 8.2.

The conclusion of pre-clinical validation of EMC/EMI, radio and coexistence verification was that the RNS® System met its intended use with the necessary contraindications, warnings, precautions, and additional information included in the labeling for the clinician and patient.

NeuroPace® Leads

The Depth and Cortical Strip Leads, components, accessories and tools were evaluated by electrical and mechanical verification testing.

Electrical and mechanical verification included:

- Connector electrical isolation per ISO 14708-1:2000, Sec. 16.3
- Voltage standoff between conductors
- Lead, components, accessories and tools geometry
- Wet rub test per ISO 14708-1:2000, Sec. 13.1
- Mechanical atmospheric pressure changes and temperature cycle per ISO 14708-1:2000, Sec. 25 and 26.2
- Lead mechanical forces during implant per ISO 14708-1:2000, Sec. 23.3
- Flexural fatigue per ISO 14708-1:2000, Sec. 23.4
- Lead implantation rigidity and fixation
- Stylet and Stylet Retainer retraction force, insertion and extraction cycling
- Suture Sleeve geometry, retraction force, and suture tensioning
- Cortical Strip Lead suture tensioning
- Lead Cap fluid seal

The NeuroPace Depth Leads and Cortical Strip Leads, and their components, accessories and tools, performed according to their specified requirements.

NeuroPace® Programmer, Remote Monitor, Patient Data Management System and Wand

The model PGM-300 Programmer, model 3302 Programmer Application Software, model DTR-300 Remote Monitor, model 3702 Remote Monitor Application Software, model W-02 Wand, Programmer and Remote Monitor components and accessories, and model 4340 Patient Data Management System (PDMS) were evaluated by electrical, mechanical and software verification testing.

Software development, verification and pre-clinical validation of the Programmer Application Software model 3302, Remote Monitor Application Software model 3702, and Patient Data Management System model 4340 was performed in accordance with their requirement specifications. Verification included confirmation of Programmer, Remote Monitor and Patient Data Management System security and access controls.

Electrical and mechanical verification of the Wand included:

- Leakage current and dielectric strength of insulation per CEI/IEC 60601-1 Second Edition 1998-12
- USB 2.0 protocol compliance
- Telemetry communication protocol compliance
- Temperature, humidity, liquid ingress and mechanical stresses per CEI/IEC 60601-1 Second Edition 1998-12
- Hardware requirements verification
- Wand model W-02 drop test

The Programmer, Remote Monitor, Wand, and their components and accessories, performed according to their specified requirements.

1.8.1.3 Biocompatibility

The implantable portions of the RNS® System employ known implantable materials generally considered to be biocompatible and safe for permanent implant use. Biocompatibility testing included the following for tissue/bone contacting materials used in the implantable RNS® System products, components, and accessories:

- Cytotoxicity (MEM Elution)
- Sensitization (ISO Guinea Pig Maximization)
- Irritation (ISO Intracutaneous Reactivity)
- Systemic Toxicity (ISO Acute Systemic Toxicity and Material-Mediated Pyrogenicity)
- Genotoxicity (Salmonella Reverse Mutation Assay, Mouse Lymphoma Assay, Chromosomal Aberration Analysis)
- Intramuscular Implantation

The following testing has been conducted for tissue contacting materials used in the non-implantable RNS® System tools:

- Cytotoxicity (MEM Elution)
- Sensitization (ISO Guinea Pig Maximization)
- Irritation (ISO Intracutaneous Reactivity)

1.8.1.4 Shelf Life, Packaging and Sterilization Information

Shelf life, packaging validation tests and sterilization validation tests were also successfully completed per recognized standards. In addition, pyrogenicity is evaluated according to the Endotoxin – LAL turbidimetric method for the implantable products, components, accessories, and surgical tools.

Shelf life for the RNS® Neurostimulator has been established as 9 months from the date the battery is attached. All other sterile products including the Connector Cover Kit, Craniectomy Template Kit, Ferrule Kit, Cranial Prosthesis Kit, NeuroPace® Lead and Lead Accessory Kits have a three year shelf life from the date of sterile packaging.

1.8.2 Animal Studies

Significant evidence of the therapeutic effect of brain stimulation for the treatment of epilepsy is derived primarily from humans. No specific animal tests were conducted regarding the use of the RNS® System for the treatment of epilepsy. Animal testing was conducted to evaluate the Leads in a chronic animal model. The study was designed as a means to collect *in vivo* data regarding the safety and biocompatibility of the NeuroPace® Depth and Cortical Strip Leads in a simulated use condition. Chronic neural tissue responses were evaluated histologically in sheep implanted with NeuroPace® Leads. Electrocorticographic recordings from sheep were reviewed to determine whether the Leads met their intended use for long-term monitoring of electrical brain activity.

Study Duration

The chronic implant duration of 11 sheep ranged from 33 days to 200 days, with a mean of 131 days. A total of 7 sheep had implant durations of 167 or more days. The changes observed and noted during the histopathology were as expected with implantation of an object into the sheep brains. The chronic animal tissue reactions noted were indicative of long-term reactions.

Biocompatibility Results

The NeuroPace® Depth Leads resulted in reactions that appeared to be consistent with changes observed in human cortectomy specimens from individuals who had depth electrodes implanted prior to the cortical resection for the treatment of complex partial onset seizures. Similar results have also been published for autopsy studies performed following chronic implantation of electrodes for deep brain stimulation. The NeuroPace® Cortical Strip Leads resulted in a response indicative of any foreign material within tissues as very commonly seen when foreign material enters the brain. In comparison to a large number of human and animal specimens, the neuronal density appeared normal under the NeuroPace® Cortical Strip Leads with no detectable cytoarchitectural changes. These results support the biocompatibility of the NeuroPace® Leads.

Electrical Recording Analysis

Recordings of electrical brain activity collected after various durations of implantation (ranging 1 week to 25 weeks post-implant) were compared from both NeuroPace® Depth Leads and NeuroPace® Cortical Strip Leads.

For the 30 recordings examined in this protocol , the magnitudes of the signals provided sufficient characterization of brain activity for monitoring purposes of both qualitative (e.g., visual assessment of ictal activity) and quantitative (e.g., detection of epileptiform activity) nature. No evidence of electrode-to-tissue sensor block was observed.

The stimulation results support the intended use of the NeuroPace® Leads for long-term use. The results of this study support the safe use of the RNS® Neurostimulator and NeuroPace® Leads to sense and record epileptiform activity from intracranial electrodes, and to deliver responsive stimulation to the brain to interrupt the detected pattern.

1.8.3 Published Studies

The long-term safety of chronic stimulation using depth leads in deep brain structures and strip leads on the cortex are supported by experience in persons treated for movement disorders, epilepsy, pain and depression that have demonstrated that the risks of electrical stimulation of the brain are low if current densities are below a threshold of 50 microCoulombs/cm^2/phase.[1,2,3] These studies have utilized depth and cortical strip leads similar to the NeuroPace® Leads, and used stimulation parameters similar to those that are provided by the RNS® System in the clinical investigations in epilepsy. The NeuroPace® RNS® Neurostimulator programmable stimulation parameters are limited by the Programmer and cannot exceed a charge density limit of 25 microCoulombs/cm^2/phase. The RNS® Neurostimulator with the NeuroPace® Leads provides the following stimulation parameters:

Electrode Surface Area	0.08 cm^2
Pulse Width per Phase	40 - 1000 microseconds
Amplitude (current controlled)	0.5 - 12 mA
Charge Density (limited by Programmer)	25 microCoulombs/cm^2/phase
Frequency	1 - 333 Hz
Burst Duration	10 – 5000 ms

An essential difference between stimulation applied by the RNS® System and that applied in studies of continuous stimulation is that the RNS® System delivers stimulation responsively. Stimulation bursts delivered by the RNS® System are typically 100 to 200 msec in duration so that total daily stimulation delivered ranges from seconds to minutes per day. Intermittent stimulation may pose fewer risks to neural tissue than continuous stimulation.

1 Fontaine D, Hamani C, Lozano A. "Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature". J Neurosurg. 2009; 110: 251-256.
2 Grill WM. "Safety considerations for deep brain stimulation: review and analysis". Expert.Rev Med.Devices 2005; 2: 409-420.
3 McCreery DB, Agnew WF, Yuen TG, Bullara L. "Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation". IEEE Trans.Biomed.Eng 1990; 37: 996-1001.

1.9 Summary of Clinical Studies

Epilepsy is a common neurological disorder that affects as many as 1 in 100 people. Epilepsy is characterized by recurrent clinical seizures, which result from disturbances in the normal electrical activity of the brain. Partial onset seizures, the most common type of seizures in adults, are the kinds of seizures that start in one part of the brain. Even though these seizures start in one part of the brain, the seizures may spread to involve most of the brain. Symptoms of a seizure may include altered awareness, extreme confusion, odd feelings, déjà vu, staring into space, altered vision, speech difficulties, sudden shaking, passing out, and/or convulsions.

Antiepileptic drugs, the Vagus Nerve Stimulator (VNS) and neurosurgical procedures such as brain resection have been used to treat disabling seizures due to epilepsy. Stimulation of the brain has been proposed as a nondestructive and reversible therapy for epilepsy in persons whose seizures cannot be controlled with antiepileptic medications. The NeuroPace® RNS® System is designed to monitor brain electrical activity and to deliver stimulation directly to the seizure focus (the part of the brain where the seizures start) when abnormal electrical activity (as defined by the physician) occurs.

NeuroPace® has conducted the following studies to support the use of the RNS® System for the treatment of partial onset seizures that are refractory to antiepileptic medications:

RNS® System Feasibility Clinical Investigation (Section 1.9.1.1.1)

This multi-center prospective clinical study conducted in the United States was designed to demonstrate adequate safety and evidence of effectiveness for the RNS® System to support the commencement of the Pivotal Clinical Investigation. The baseline (pre-implant) data for the Feasibility study was provided by the nonsignificant risk Prospective Seizure Frequency (PSF) study. For ease of understanding, the combined data are simply presented as Feasibility study data throughout this document.

The safety results of the Feasibility study are presented within the combined safety analysis (**Section 1.9.3.2**). The effectiveness data in this primarily open label study were used only in the analyses to provide evidence of sufficient efficacy to support commencement of the Pivotal study.

RNS® System Pivotal Clinical Investigation (Section 1.9.1.1.2)

This multi-center prospective randomized, double-blinded, sham-stimulation controlled clinical study conducted in the United States was designed to assess safety and to demonstrate that the RNS® System is effective as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

The effectiveness results are presented in **Section 1.9.3.1**. The safety results of the study are presented within the combined safety analysis (**Section 1.9.3.2**).

RNS® System Long-term Treatment Clinical Investigation (LTT) (Section 1.9.1.1.3)

This multi-center prospective open label clinical study conducted in the United States was designed to assess the ongoing safety and to evaluate the long-term effectiveness of the RNS® System. Subjects having completed the Feasibility or Pivotal clinical investigation were potential candidates for the LTT study.

The safety data collected during this ongoing study are presented within the combined safety analysis (**Section 1.9.3.2**). The effectiveness endpoint analyses for this ongoing study have not been completed.

1.9.1 Study Designs and Methods

1.9.1.1 Study Designs and Timelines

1.9.1.1.1 FEASIBILITY STUDY

The Feasibility study was a multi-center clinical investigation of individuals with medically intractable epilepsy. Sixty five subjects were implanted with the RNS® Neurostimulator and Leads in the Feasibility study.

Eligible subjects were 18-65 years of age with medically intractable partial onset seizures and a minimum of 4 simple partial seizures (motor or sensory), complex partial seizures, and/or secondarily generalized seizures in each of the previous three months. Subjects were required to be on a stable antiepileptic medication regimen and must have previously undergone diagnostic testing that localized one or two epileptogenic region(s). Subjects with psychogenic or non-epileptic seizures, status epilepticus, active psychosis, severe depression, or suicidal ideation within the preceding year were excluded.

The first four subjects implanted with the RNS® Neurostimulator and Leads at a clinical site participated in an open label protocol (all subjects received responsive stimulation), and subsequent subjects at that site participated in a randomized, double-blind, concurrent sham-stimulation control protocol in which the Treatment group received stimulation and Sham group did not. Following completion of the 12 week Evaluation Period, subjects transitioned to an Open Label Period, and all subjects were able to receive responsive stimulation. Subjects continued in the Open Label Period through the end of study participation, which was 2 years post-implantation (**Figure 1-1**).

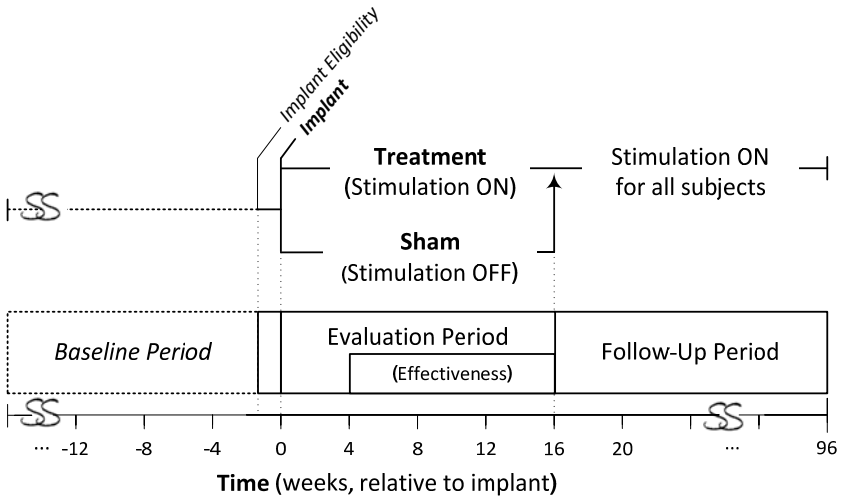


Figure 1-1: RNS® System Feasibility Clinical Investigation – Trial Flow and Periods

1.9.1.1.2 PIVOTAL STUDY

The RNS® System Pivotal Clinical Investigation was a randomized, double-blinded, multi-center, sham-controlled clinical investigation of individuals with medically intractable partial onset seizures. In total, 191 subjects were implanted with the RNS® Neurostimulator and Leads in the Pivotal study.

Eligible subjects were 18-70 years of age with medically intractable partial onset seizures and an average of three or more disabling seizures per month over the three most recent months, with no month with less than two seizures. Subjects were required to be on a stable antiepileptic medication regimen and must have previously undergone diagnostic testing that localized one or two epileptogenic region(s). Subjects with psychogenic or non-epileptic seizures, status epilepticus, active psychosis, severe depression, or suicidal ideation within the preceding year were excluded.

The investigation had five periods: the Baseline Period, Post-Operative Stabilization Period, Stimulation Optimization Period, Blinded Evaluation Period, and Open Label Period (**Figure 1-2**).

To qualify for implantation with the RNS® Neurostimulator and Leads, the subjects were required to remain on a stable AED regimen while having an average of three or more disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures) per month over three consecutive months during the Baseline Period, with no month with less than two seizures.

Subjects were implanted with the RNS® Neurostimulator and Leads within 28 days following the date of qualification for implantation of the RNS® Neurostimulator and Leads. Subjects were randomized 1:1 at the end of the Post-Operative Stabilization Period (4 weeks post-implant). Subjects randomized to the Treatment group received responsive stimulation during the Stimulation Optimization and Blinded Evaluation Periods; subjects

randomized to the Sham group did not receive responsive stimulation during these periods. Following completion of the Blinded Evaluation Period (20 weeks post-implant), subjects transitioned to the Open Label Evaluation Period and both Treatment and Sham group subjects were able to receive responsive stimulation.

A schematic of the study timeline is provided in **Figure 1-2**. The primary effectiveness analysis compares changes in seizure frequency in the Treatment group and in the Sham group during the 12 week Blinded Evaluation Period relative to the 12 week Pre-Implant Period. The Pre-Implant Period (not shown in the figure) is defined as the 12 weeks in the Baseline Period leading up to and including the date of qualification for implantation. Primary safety analyses include adverse event data over the first 12 weeks post-implantation. Secondary safety and effectiveness analyses include data from the Blinded Evaluation and Open Label Evaluation Periods.

Information regarding daily seizure counts, subject safety and subject well-being was collected by a physician investigator who was blinded to the subject's randomization status and a second non-blinded physician investigator was responsible for Neurostimulator programming.

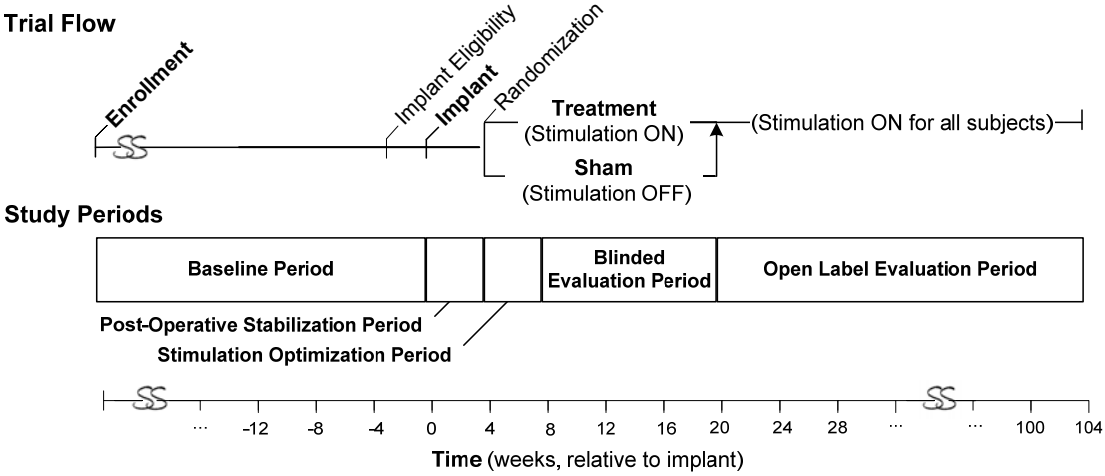


Figure 1-2: RNS® System Pivotal Clinical Investigation – Trial Flow and Periods

1.9.1.1.3 LONG-TERM TREATMENT STUDY

The RNS® System Long-term Treatment Clinical Investigation (LTT) is an on-going open label, multi-center, prospective clinical investigation of individuals with medically intractable, partial onset epilepsy. Subjects could enroll in the LTT study once they had completed the RNS® System Feasibility or Pivotal clinical investigations; 230 subjects did so. During the LTT study, subjects can continue to receive responsive stimulation. Each subject participates for a maximum of 7 years. Data regarding safety and effectiveness are collected at 6-month intervals, and data regarding quality of life are collected at yearly intervals. Antiepileptic drug adjustments are permitted as needed.

1.9.1.2 Statistical Methods

1.9.1.2.1 Effectiveness (Pivotal Study Only)

The primary effectiveness objective for the Pivotal study is to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the Treatment group compared to the Sham group during the Blinded Evaluation Period relative to the Pre-Implant Period.

Seizure frequency was modeled using the generalized estimating equations (GEE) method, which accounts for within subject correlations and variability across subject populations. The model assumes a negative binomial distribution and includes clinical covariates. The primary effectiveness endpoint variable is the Group-by-Time interaction term in the GEE model, where Group refers to active stimulation (Treatment) or sham stimulation (Sham) and Time refers to the Pre-Implant Period or Blinded Evaluation Period.

A significant and negative Group-by-Time interaction term demonstrates a significantly greater reduction in seizure frequency in the Treatment group than the Sham group during the Blinded Evaluation Period compared to the Pre-Implant Period.

1.9.1.2.2 Safety (Combined RNS® System Studies)

The primary safety endpoint variables for the Feasibility and Pivotal studies were the serious adverse event (SAE) rates during the Acute Period (initial implant procedure and the following month) and the Short-Term Chronic Period (initial implant procedure and the following three months). The SAE rate is defined as the proportion of subjects having a serious adverse event. The SAE rate includes all SAEs whether reported as device-related or not.

Other safety analyses (for all RNS® System studies) consider the rate of occurrence of any adverse event during any period of the study. Rates of adverse events are described by the percentage of subjects experiencing one or more serious or mild adverse events.

An additional safety objective (for all the RNS® System studies) is to collect data on the frequency of Sudden Unexplained Death in Epilepsy (SUDEP) and upon completion of the clinical investigation estimate the SUDEP rate as a ratio of the number of events in subjects programmed to receive stimulation/total number of patient stimulation years, with a 95% confidence interval calculated according to patient stimulation years.

1.9.2 Description of Subject Population

1.9.2.1 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the Feasibility and Pivotal studies were similar (the key inclusion and exclusion criteria for the studies are presented in **Table 1-1** and **Table 1-2**). The key differences between studies were:

- The Feasibility study included simple partial sensory seizures as a qualifying seizure type, whereas the Pivotal study did not include simple partial sensory seizures as a qualifying seizure type.

- The Feasibility study required a minimum of 4 seizures per month (including simple partial sensory seizures), whereas the Pivotal study required an average of 3 seizures per month (excluding simple partial sensory seizures).
- The Feasibility study included individuals between ages 18 and 65 and the Pivotal study included individuals between ages 18 and 70.

Table 1-1: Key Inclusion Criteria

Inclusion Criteria	Feasibility Study	Pivotal Study
Subject has simple partial motor seizures, complex partial seizures and/or secondarily generalized seizures	Yes[1]	Yes
Seizure counts per month	4 or more[2]	average of 3 or more[3]
Age	18-65 years	18-70 years
Subject has seizures that are severe enough to cause injuries or significantly impair functional ability in domains including employment, psychosocial, education and mobility.	Yes	Yes
Subject has seizures that are distinct, stereotypical events that can be reliably counted	Yes	Yes
Subject failed treatment with a minimum of two antiseizure medications (used in appropriate doses) with adequate monitoring of compliance and the effects of treatment.	Yes	Yes
Subject has remained on the same antiseizure medication(s) over the preceding three (3) months	Yes	Yes
Subject has undergone diagnostic testing that has established the epileptiform activity onset region(s)	Yes	Yes, with no more than 2 epileptogenic regions

1 The Feasibility study also included simple partial sensory seizures.
2 Subject has a minimum of four (4) or more countable seizures every month over the last three (3) months.
3 Subject has an average of three or more disabling seizures per month (28 days) over the three most recent months, with no month with less than two seizures.

Table 1-2: Key Exclusion Criteria

Exclusion Criteria	Feasibility Study	Pivotal Study
Subject has been diagnosed with psychogenic or non-epileptic seizures in the preceding year.	Yes	Yes
Subject has been diagnosed with primarily generalized seizures.	Yes	Yes
Subject has experienced unprovoked status epilepticus in the preceding year.	Yes	Yes
Subject has a clinically significant or unstable medical condition or a progressive central nervous system disease.	Yes	Yes
Subject has been diagnosed with active psychosis, severe depression or suicidal ideation in the preceding year.	Yes	Yes
Subject has an implanted Vagus Nerve Stimulator (VNS).	Yes[1]	Yes[2]
Subject has had therapeutic surgery to treat epilepsy	in the preceding year	in the preceding 6 months
Subject is implanted with an electronic medical device that delivers electrical energy to the head.	Yes	Yes
Subject requires repeat MRIs	Yes	in which the head is exposed to the radio frequency field

1 A subject with an inactive VNS could be enrolled so long as the VNS was explanted prior to or at the same time as the RNS® System implant.
2 A subject could be enrolled if the subject is willing to have the VNS explanted (excluding leads) prior to or at the time of the RNS® System implant. (Subjects with VNS devices must have had VNS therapy discontinued for at least three months prior to enrollment.)

Subjects were eligible to enroll into the LTT study if they had completed either the Feasibility or Pivotal studies, had the RNS® System implanted, had elected to continue to receive responsive stimulation, and were able to attend scheduled appointments for the study. They were not eligible if they had an active psychiatric or mental illness that made it inadvisable for the subject to continue to receive responsive stimulation or if the subject had been diagnosed with psychogenic or non-epileptic seizures, or primarily generalized seizures during the Feasibility or Pivotal studies.

1.9.2.2 Subject Accountability and Analysis Population

Subject participation in the Feasibility, Pivotal and LTT studies is presented in **Figure 1-3** as of May 12, 2011.

Of the 256 implanted subjects, 22 subjects discontinued the Feasibility or Pivotal studies and 21 discontinued the LTT study. Reasons for discontinuations include adverse events which resulted in explant (8), subject preference (20) and physician preference (1), lost to follow-up (3), death (9) and reasons unknown (2). The adverse events included 7 due to infection and one as a result of a cerebral hemorrhage.

Analysis Populations

The safety and effectiveness analysis populations for the Pivotal study included all 191 subjects implanted and randomized; this is the intent-to-treat population. The pooled safety analysis population includes the intent-to-treat safety population from the RNS® System Feasibility, Pivotal and Long-term Treatment (LTT) Clinical Investigations combined. This includes all 256 subjects implanted with the RNS® Neurostimulator and Leads.

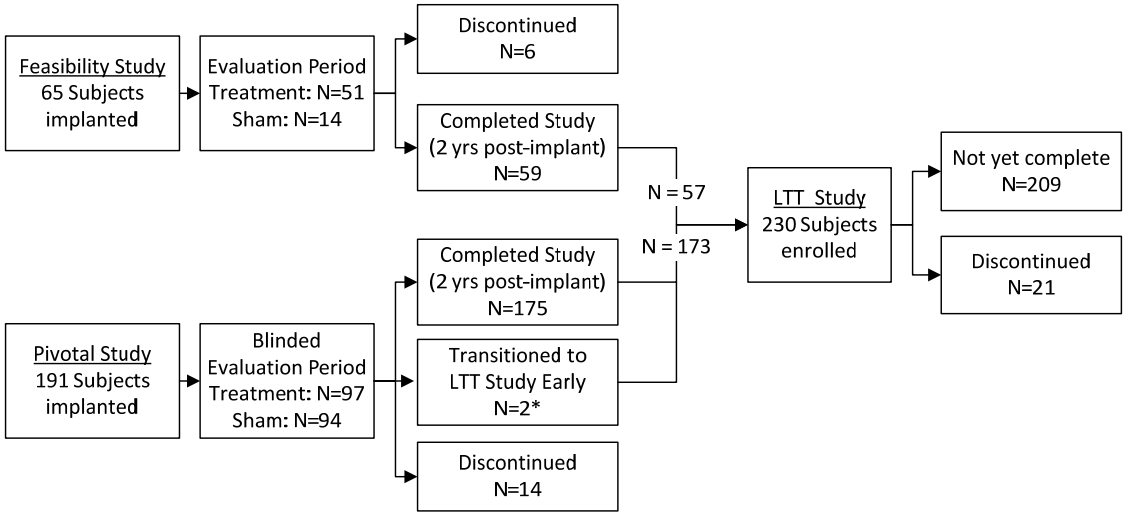


Figure 1-3: Patient Flow Diagram

* Two subjects withdrew early (discontinued) from the Pivotal study to undergo resective epilepsy surgery. Waivers were granted to allow enrollment into the LTT study so that the subjects could continue to receive responsive stimulation to treat seizures arising from the non-resected seizure focus.

1.9.2.3 Demographics and Baseline Characteristics

Demographic information for subjects implanted in the Feasibility and Pivotal studies is presented in **Table 1-3**. All subjects participating in the LTT study originally enrolled in the Feasibility or Pivotal study.

Table 1-3: Demographics

Characteristic	All (N = 256)	By Study	
		Feasibility (N = 65)	Pivotal (N = 191)
Gender (percent female)	49% (125/256)	52% (34/65)	48% (91/191)
Age in years[1] (average, SD , range)	34.0 ± 11.4 (18 - 66)	30.9 ± 10.3 (18 - 56)	34.9 ± 11.6 (18 - 66)
Years with epilepsy (average, SD, range)	19.6 ± 11.4 (2 - 57)	17.0 ± 10.1 (2 - 42)	20.5 ± 11.6 (2 - 57)
Number of AEDs (average, SD, range)	2.9 ± 1.1 (0 - 8)	2.9 ± 1.0 (1 - 6)	2.8 ± 1.2 (0 - 8)
Seizures per month (average, SD, range, median)	50.7 ± 177.4 (0 – 2320) median = 10.2	99.2 ± 332.8 (0 – 2320) median = 11.3	34.2 ± 61.9 (3 – 338) median = 9.7

1 Due to hospital confidentiality requirements some institutions did not provide date of birth for subjects

1.9.3 Results – Effectiveness and Safety

1.9.3.1 Effectiveness Results

Effectiveness of the RNS® System was established by the primary effectiveness analysis in the Pivotal study which demonstrated that the Treatment group (receiving responsive stimulation) experienced a significantly greater reduction in total disabling seizures compared to the Sham group (not receiving stimulation) during the Blinded Evaluation Period compared to the Pre-Implant Period of the investigation. Further support for the effectiveness is provided by the Open Label Period of the Pivotal study, which demonstrated a sustained reduction in the frequency of disabling seizures. Another measure of effectiveness was quality of life. Quality of life overall was significantly improved at the end of the evaluation period and over the Open Label Period compared to the baseline, as were a number of domains of quality of life concerned with social function, cognition, health discouragement and seizure worry.

Primary Effectiveness Endpoint

The primary effectiveness endpoint of the RNS® System Pivotal Clinical Investigation was met, demonstrating that the reduction in seizure frequency of subjects randomized to receive responsive stimulation during the Blinded Evaluation Period (Treatment group) was significantly greater than that experienced by subjects randomized to receive sham stimulation (Sham group). Over the entire Blinded Evaluation Period, the Treatment group had a reduction in seizure frequency of 37.9% compared to a 17.3% reduction in the Sham group; this difference is statistically significant (p = 0.012, GEE).

In the first month after implantation of the RNS® Neurostimulator and Leads, prior to enabling stimulation in either the Treatment or Sham group, both groups experienced a reduction in seizures. Whether this is an effect of the surgical procedure, anesthesia or of an effect of lead implantation is not known. However, the reduction in seizure frequency in the Sham group began to abate by the fourth post-operative month. By the fifth month post-implant (the third month of the Blinded Evaluation Period), the Sham group had returned to their pre-implant seizure frequency, whereas the Treatment group continued to experience a progressive reduction in disabling seizures (**Figure 1-4**). As estimated from the GEE model, by the third month of the Blinded Evaluation Period, the Treatment group experienced a 41.5% reduction in seizure frequency compared to only a 9.4% reduction in the Sham group ($p = 0.008$).

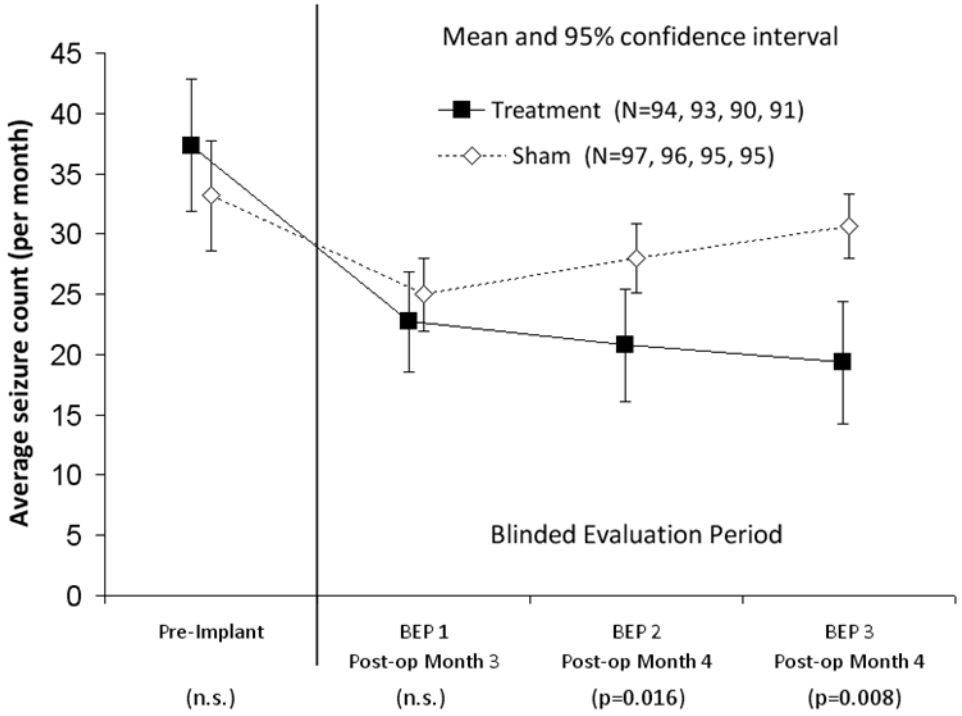


Figure 1-4: Mean Disabling Seizures
Pre-Implant Period through Blinded Evaluation Period

[N represents the number of subjects for which any seizure data are available during that interval; BEP = Blinded Evaluation Period; n.s. = not significant]

Reduction in Seizure Frequency

There was a significant reduction in mean seizure frequency in the Treatment group over the entire the Blinded Evaluation Period compared to their Pre-Implant Period seizure frequency. When evaluated by month, there is a significant difference between the Treatment and Sham groups during the second and third months of the Blinded Evaluation Period (months 3-4 and 4-5 post-implant in **Figure 1-4** above), when the effect of the surgery and/or temporary implant effect abated. Over the entire Blinded Evaluation Period, the Treatment group experienced a mean reduction of over 11 seizures per month ($p < 0.001$) while the Sham group experienced a reduction of 5 seizures per

month (not significant). By the third month of the Blinded Evaluation Period, the mean seizure frequency reduction in the Treatment group reached 12 seizures per month while the Sham group had a reduction of less than 1 seizure per month (difference in reduction between Treatment and Sham groups is significant, $p < 0.001$). In addition, by the third month of the Blinded Evaluation Period, subjects in the Treatment group also experienced 27% fewer days with seizures than during their pre-implant baseline.

Open Label Period and Long-term Follow-up

The seizure reduction in subjects in the Sham group when responsive stimulation is first enabled further demonstrates the effectiveness of responsive stimulation. When subjects in the Sham group first received responsive stimulation in the Open Label Period, there was an immediate reduction in seizure frequency (**Figure 1-5**). The reduction in mean seizure frequency in the Sham group over a 3-month period, beginning one month after stimulation had been enabled (months 7-9) is significant relative to their Pre-Implant Period ($p = 0.04$). This translates to a reduction of nearly 8 seizures per month. The reduction in seizures can be attributed to a favorable effect of stimulation, not an implant or placebo effect. The implant effect had largely resolved in the Sham subjects by the end of the Blinded Evaluation Period. This response was also unlikely to be a placebo effect. Subjects in the Sham group did not know whether they had been receiving stimulation during the Blinded Evaluation Period, since randomization group was not disclosed to subjects during the entire Pivotal study.

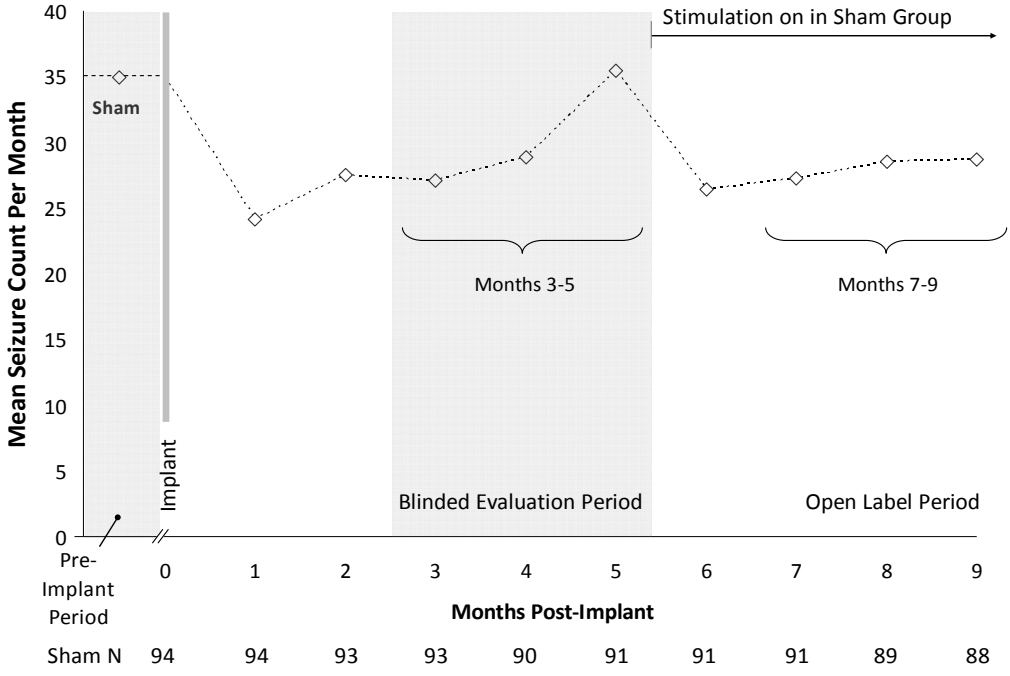
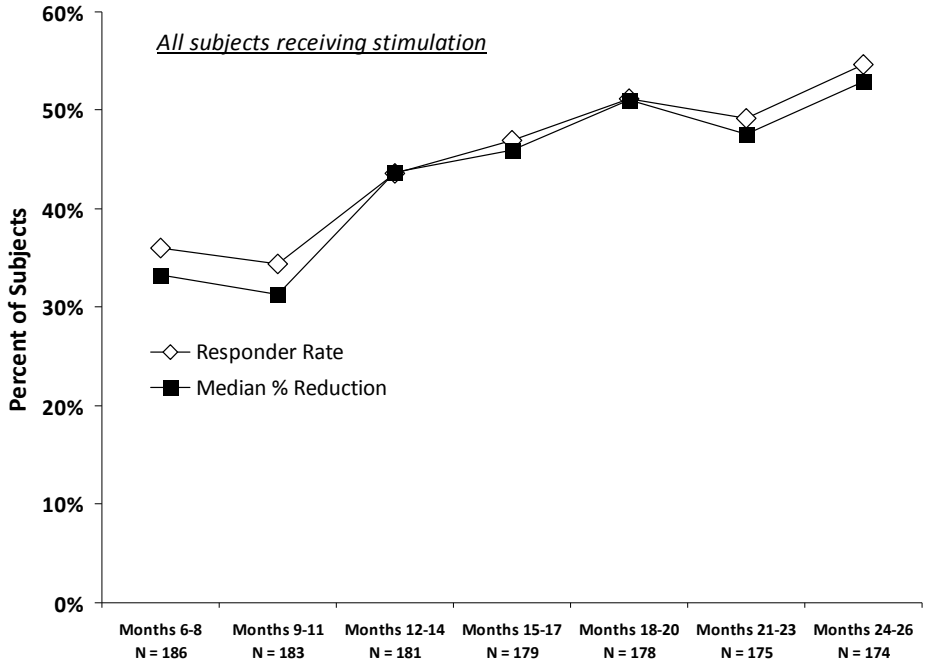


Figure 1-5: Pivotal Study – Mean Seizure Frequency by Month Pre-Implant Period through Month 9 Post-Implant (Sham Group)

[N represents the number of subjects in the Sham group for which any seizure data are available during that interval]

As of the data cutoff date, over 80% of all subjects in the Open Label Period experienced some reduction in seizure frequency, and 54% of subjects experienced at least a 50% or greater reduction in seizure frequency. Additionally, the effectiveness of responsive stimulation is sustained, and even improves, over time (**Figure 1-6**). For those subjects who have reached 2 years post-implant, 55% of the subjects experienced a 50% or greater reduction in seizures.



Includes all subjects for whom any data are available for each 3 month period.

Figure 1-6: Responder Rate and Median Percent Reduction in Seizure Frequency during the Open Label Period

Quality of Life

The reduction in seizures with responsive stimulation is clinically meaningful as demonstrated by significant improvements in quality of life. Subjects in the study had lower than overall quality of life compared to established norms for persons with moderate to severe epilepsy. At 1 and 2 years after implantation, there were statistically significant group improvements in quality of life overall and in 9 of the 17 primary scale scores, indicating that subjects had a more positive perception of their cognitive function, relationships and social function, overall health and vulnerability to seizures. There were clinically significant improvements in quality of life for 38% (63/166) of subjects at one year post-implant and for 44.2% (68/154) at 2 years post-implant. 40% of subjects or more showed clinically significant improvement in the scales of memory, attention/concentration, health discouragement, and seizure worry at one and two years.

1.9.3.2 Safety Results

The RNS® System Feasibility, Pivotal and Long-term Treatment studies evaluated the safety of the RNS® System for epilepsy in 256 implanted subjects over 903 patient years of implant experience and 819 patient years of responsive stimulation. There were no unanticipated device-related serious adverse events during the RNS® System studies. Acute and short term chronic adverse events compared favorably to comparable procedures as demonstrated by the primary safety endpoint. There was no difference between the Treatment and Sham groups in the overall percentage of subjects experiencing an adverse event, or any specific type of adverse event during the evaluation periods of the studies. The overall rate of adverse events or of specific adverse events does not increase over time, whether device-related or not device-related. This experience demonstrates that the risks of implantation of the RNS® Neurostimulator and Leads are low, that stimulation is well tolerated, and that responsive stimulation is safe over time.

1.9.3.2.1 PRIMARY SAFETY ENDPOINT

The RNS® System Feasibility and Pivotal studies achieved the safety endpoints pre-specified in the investigational plans. The rate of serious adverse events after implantation of the Neurostimulator and Leads was favorable over the first 4 weeks (Acute Period) and in the first 12 weeks (Short-Term Chronic Period) compared to comparable procedures, which were the combined risks of implantation of intracranial electrodes for purposes of an epilepsy surgery evaluation and epilepsy surgery, and the risks of deep brain stimulation for treatment of movement disorders. The SAE rate for the Acute Period in the Pivotal study was 12%, and the SAE rate for both the Pivotal and Feasibility studies combined was 10.5%, lower than the pre-specified literature-derived comparator of 15%. The SAE rate for the Short-Term Chronic Period for the Pivotal study was 18.3%, and the SAE rate for both studies combined was 16.0%. These rates were lower than the pre-specified literature-derived comparator of 36%. These results demonstrate that the SAE rate over the first month and the first 3 months after implantation is at least comparable to the literature based historical controls.

1.9.3.2.2 ADVERSE EVENTS

Adverse events were collected for all subjects in the RNS® System studies. All data are current as of May 12, 2011. The investigator classified each adverse event as serious or mild and as device-related (includes device related and device relation uncertain) or not device-related. Adverse events were considered serious if the event resulted in significant risks or consequences to the subject's acute or long-term health, serious injury or death, hospital admission, or if invasive medical intervention was required to alleviate the adverse event. Adverse events are presented using MedDRA Coding according to the PT = Preferred Term.

1.9.3.2.2.1 Adverse Events during the Blinded Evaluation Period of the Pivotal Study

Table 1-4 presents adverse events reported in 2.5% or more of the subjects in either the Treatment or the Sham groups who entered the 12 week Blinded Evaluation Period of the Pivotal Study. This includes all adverse events whether device-related or not device-related. Only one type of adverse event was significantly different between the Treatment and Sham stimulation groups. Therapeutic agent toxicity, which refers to side effects of antiepileptic medications, was more common in the Sham group (5 subjects, all mild events) than the Treatment group (none). There were no other differences in adverse events between the Treatment group and Sham group.

Table 1-4: Pivotal Study – Adverse Events in ≥ 2.5% of Subjects in Either Group During the Blinded Evaluation Period (Treatment vs. Sham)

	Treatment (N=96)	Sham (N=93)	
Preferred Term	**% subjects with events** (# subjects)	**% subjects with events** (# subjects)	**p-value**[1]
Nasopharyngitis	6.3% (6)	8.6% (8)	0.588
Headache	5.2% (5)	7.5% (7)	0.563
Contusion (dts)	7.3% (7)	2.2% (2)	0.170
Skin laceration (dts)	6.3% (6)	3.2% (3)	0.498
Complex partial seizures increased	4.2% (4)	3.2% (3)	1.000
Depression	5.2% (5)	2.2% (2)	0.445
Dysesthesia	2.1% (2)	5.4% (5)	0.273
Influenza	4.2% (4)	3.2% (3)	1.000
Vomiting	3.1% (3)	3.2% (3)	1.000
Adverse drug reaction	3.1% (3)	2.2% (2)	0.445
Therapeutic agent toxicity	--	5.4% (5)	0.027
Upper respiratory tract infection	1.0% (1)	4.3% (4)	0.206
Pain of skin	4.2% (4)	--	0.121
Pharyngitis	1.0% (1)	3.2% (3)	0.363
Abdominal pain	3.1% (3)	--	0.246
Balance disorder	--	3.2% (3)	0.117
Head injury	--	3.2% (3)	0.117

1 Fisher's exact test

There were 4 device-related (or device relation uncertain) serious adverse events during the Blinded Evaluation Period. One subject in the Treatment group experienced an increase in complex partial seizures. One subject in the Sham group experienced three device-related serious adverse events; these were an increase in complex partial seizures, an increase in simple partial seizures (sensory), and a new type of simple partial seizure (sensory).

1.9.3.2.2.2 Adverse Events during the Pivotal Study: All Study Periods through Two Years Post-Implant

All device-related (or device relation uncertain) adverse events (serious and mild) occurring during the Pivotal study through 2 years post-implant in 2.5% or more of the subjects are presented by study period in **Table 1-5**.

Table 1-5: Pivotal Safety – Device-Related[1] Adverse Events in ≥ 2.5% of Subjects by Study Period through 2 Years

	Post Op (Implant - Week 4)	Stim Opt (Weeks 4 - 8)	Blinded Eval (Weeks 8 - 12)	Open Label Period		All Study Periods[2]
				(Weeks 20 - 52)	(Weeks 52 - Completion)	
Number of Subjects Entering (N) / Total Implant years within Interval	**191/ 14.7**	**191/ 14.6**	**189/ 43.2**	**187/ 113.4**	**182/ 193.4**	**191/ 379.2**
Preferred Term	**% subjects (# subjects)[3]**					
Implant site pain	9.9% (19)	2.1% (4)	0.5% (1)	3.7% (7)	4.4% (8)	18.3% (35)
Procedural headache	11.5% (22)	--	--	0.5% (1)	0.5% (1)	12.6% (24)
Headache	--	3.1% (6)	2.1% (4)	5.3% (10)	1.6% (3)	9.4% (18)
Complex partial seizures increased	--	--	2.1% (4)	4.3% (8)	3.8% (7)	8.9% (17)
Complex partial seizures	0.5% (1)	0.5% (1)	1.1% (2)	4.3% (8)	2.7% (5)	7.9% (15)
Dysaesthesia	--	1.0% (2)	2.1% (4)	3.7% (7)	2.7% (5)	7.9% (15)
Tonic-clonic seizures increased	--	0.5% (1)	0.5% (1)	4.3% (8)	3.3% (6)	7.9% (15)
Simple partial seizures (sensory)	1.0% (2)	1.0% (2)	1.1% (2)	2.7% (5)	1.6% (3)	6.8% (13)
Photopsia	--	1.0% (2)	--	3.7% (7)	1.6% (3)	5.8% (11)
Tonic-clonic seizures exacerbated	--	0.5% (1)	--	3.2% (6)	2.2% (4)	5.8% (11)
Complex partial seizures exacerbated	--	--	1.1% (2)	2.1% (4)	2.2% (4)	5.2% (10)
Device interaction	1.6% (3)	0.5% (1)	1.1% (2)	1.6% (3)	0.5% (1)	5.2% (10)
Memory impairment	1.0% (2)	0.5% (1)	0.5% (1)	2.1% (4)	1.1% (2)	5.2% (10)
Implant site infection	2.6% (5)	--	--	1.1% (2)	1.6% (3)	4.7% (9)
Implant site swelling	3.7% (7)	0.5% (1)	--	--	0.5% (1)	4.7% (9)
Simple partial seizures (motor)	1.0% (2)	0.5% (1)	1.1% (2)	1.1% (2)	1.1% (2)	4.2% (8)
Dizziness	1.0% (2)	1.0% (2)	--	0.5% (1)	1.1% (2)	3.7% (7)
Depression	--	0.5% (1)	1.1% (2)	1.6% (3)	0.5% (1)	3.1% (6)
Muscle twitching	1.0% (2)	1.0% (2)	0.5% (1)	0.5% (1)	0.5% (1)	3.1% (6)
Aphasia	1.0% (2)	0.5% (1)	--	--	1.1% (2)	2.6% (5)
Device lead damage	--	--	--	2.7% (5)	0.5% (1)	2.6% (5)
Implant site paraesthesia	--	0.5% (1)	1.1% (2)	--	1.1% (2)	2.6% (5)
Incision site infection	--	--	1.1% (2)	0.5% (1)	1.6% (3)	2.6% (5)
Paraesthesia	1.0% (2)	--	0.5% (1)	1.1% (2)	--	2.6% (5)

1 Device-related includes events categorized as device-relation uncertain
2 Row totals may not sum to totals in this column because some subjects may have had SAEs in more than one period
3 % subjects = # subjects with event / number of subjects entering interval

The most frequent serious adverse event during the 28 days after implant was implant site infection, occurring in 2.6% of subjects. There were 5 implant site infections; one of these subjects had the Neurostimulator and

Leads explanted. The most common non-serious adverse events were implant site pain, procedural headache and implant site swelling.

In the Pivotal study the most common device-related serious adverse events through two years post-implant were implant site infection (3.7%), increased complex partial seizures (3.1%), device lead damage (2.6%), increased tonic-clonic seizures (2.6%), and device lead revision (2.1%). Device-related serious adverse events affecting 1% (2 subjects) were exacerbated complex partial seizure, suicidal depression, extradural hematoma, hydrocephalus, post-ictal state, premature battery depletion, skin laceration (due to seizure), and subdermal hematoma (due to seizure).

Device-related serious adverse events affecting 0.5% (1 subject) at any time over the entire Pivotal Study were acquired epileptic aphasia, apraxia, cerebral hemorrhage, convulsive status epilepticus, death, dysphemia, EEG monitoring, headache, implant site discharge, implant site erosion, implant site pain, intracranial hypotension, medical device removal, nonconvulsive status epilepticus, procedural headache, new simple partial seizures (sensory), increased simple partial seizures (sensory), subdural hematoma, suture related complication, and exacerbated tonic-clonic seizures.

1.9.3.2.2.3 Device-Related Serious Adverse Events by Year (Combined RNS® System Studies)

Device-related serious adverse events that occurred at any time after implantation of the Neurostimulator and Leads in subjects in the Feasibility, Pivotal and Long-term Treatment studies are presented in order of decreasing frequency in **Table 1-6**. Adverse events are presented by year from the first through five years post-implant. Adverse events that occurred after the fifth year are included in the total (All Study Periods). The most frequent device-related serious adverse events (occurring in ≥ 2.5% of subjects) were implant site infection (5.9%), premature battery depletion (which required a surgical procedure) (4.3%), followed by an increase in tonic-clonic seizures (3.9%) medical device removal (3.5%), increase in complex partial seizures (3.1%), and device lead damage (2.7%).

Table 1-6: Combined Safety – Device-Related Serious Adverse Events by Year

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods [1]
# of subjects entering year / Implant years within Interval	**256 / 249.9**	**246 / 240.1**	**235 / 188.6**	**148 / 112.2**	**85 / 60.6**	**256 / 903.4**
Preferred Term	**% Subjects (# subjects) [2]**					
Implant site infection	2.3% (6)	0.4% (1)	2.1% (5)	1.4% (2)	--	5.9% (15)
Premature battery depletion	1.6% (4)	2.4% (6)	0.4% (1)	--	--	4.3% (11)
Tonic-clonic seizures increased	1.2% (3)	1.6% (4)	0.9% (2)	0.7% (1)	--	3.9% (10)
Medical device removal	0.4% (1)	1.2% (3)	0.9% (2)	0.7% (1)	1.2% (1)	3.5% (9)
Complex partial seizures increased	2.7% (7)	0.8% (2)	--	--	--	3.1% (8)
Device lead damage	2.0% (5)	0.4% (1)	0.9% (2)	--	--	2.7% (7)
EEG monitoring	0.4% (1)	--	0.9% (2)	--	1.2% (1)	2.0% (5)

Table 1-6: Combined Safety – Device-Related Serious Adverse Events by Year

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods [1]
Cerebral hemorrhage	0.4% (1)	--	1.3% (3)	--	--	1.6% (4)
Device lead revision	0.4% (1)	1.2% (3)	--	--	--	1.6% (4)
Implant site erosion	0.4% (1)	0.4% (1)	--	0.7% (1)	--	1.6% (4)
Complex partial seizures exacerbated	0.8% (2)	--	0.4% (1)	--	--	1.2% (3)
Death	0.4% (1)	0.4% (1)	--	0.7% (1)	--	1.2% (3)
Depression suicidal	0.8% (2)	--	--	--	1.2% (1)	1.2% (3)
Extradural hematoma	0.8% (2)	--	--	--	--	0.8% (2)
Headache	0.4% (1)	0.4% (1)	--	--	--	0.8% (2)
Hydrocephalus	0.8% (2)	--	--	--	--	0.8% (2)
Nonconvulsive status epilepticus	0.8% (2)	--	--	--	--	0.8% (2)
Postictal state	0.8% (2)	--	--	--	--	0.8% (2)
Simple partial seizures increased (sensory)	0.4% (1)	--	0.4% (1)	--	--	0.8% (2)
Skin laceration (dts)	0.4% (1)	0.4% (1)	--	--	--	0.8% (2)
Subdural haematoma (dts)	0.4% (1)	0.4% (1)	--	--	--	0.8% (2)
Tonic-clonic seizures exacerbated	0.4% (1)	0.4% (1)	--	--	--	0.8% (2)
Acquired epileptic aphasia	0.4% (1)	--	--	--	--	0.4% (1)
Agitation	--	--	0.4% (1)	--	--	0.4% (1)
Apraxia	0.4% (1)	--	--	--	--	0.4% (1)
Complex partial seizures	--	--	0.4% (1)	--	--	0.4% (1)
Confusional state	0.4% (1)	--	--	--	--	0.4% (1)
Convulsive status epilepticus	--	0.4% (1)	--	--	--	0.4% (1)
Cranioplasty	--	--	--	0.7% (1)	--	0.4% (1)
Device electrical finding[3]	--	--	--	0.7% (1)	--	0.4% (1)
Device malfunction[4]	--	--	--	0.7% (1)	--	0.4% (1)
Dysphemia	0.4% (1)	--	--	--	--	0.4% (1)
Head injury (dts)	--	--	0.4% (1)	--	--	0.4% (1)
Implant site discharge	0.4% (1)	--	--	--	--	0.4% (1)
Implant site pain	--	0.4% (1)	--	--	--	0.4% (1)
Intracranial hypotension	--	0.4% (1)	--	--	--	0.4% (1)
Procedural headache	0.4% (1)	--	--	--	--	0.4% (1)
Simple partial seizures increased (motor)	0.4% (1)	--	--	--	--	0.4% (1)
Simple partial seizures (sensory)	0.4% (1)	--	--	--	--	0.4% (1)
Stitch abscess	--	--	0.4% (1)	--	--	0.4% (1)
Suicidal ideation	--	--	0.4% (1)	--	--	0.4% (1)
Suicide attempt	0.4% (1)	--	--	--	--	0.4% (1)
Subdural hematoma	0.4% (1)	--	--	--	--	0.4% (1)
Suture related complication	--	0.4% (1)	--	--	--	0.4% (1)
Summary of SAEs by Year[5]	15.6% (40)	12.2% (30)	8.1% (19)	6.1% (9)	3.5% (3)	32.8% (84)

1 Row totals may not sum to totals in this column because some subjects may have had SAEs in more than one period. Events beyond year 5 are only included in the total.

2 % Subjects = # subjects with event / number of subjects entering interval

3 Device electrical finding: the battery appeared to be depleting faster than anticipated so was replaced. However, when explanted, the NeuroPace product investigation determined that the device performed as designed.

4 Device malfunction: subject was unable to interrogate the Neurostimulator after being assaulted in the head so the Neurostimulator was replaced. Post-implant investigation showed normal Neurostimulator function.

5 Column totals may not sum to totals in this row because some subjects may have had more than one SAE type

Year 1 (implant - Week 52), Year 2 (Weeks 52 - 104), Year 3 (Weeks 104 - 156), Year 4 (Weeks 156 - 208), Year 5 (Weeks 208 - 260)

1.9.3.2.2.4 Adverse Events of Particular Relevance (Combined RNS® System Studies)

Adverse events of particular relevance in persons with epilepsy and in persons with an implanted medical device include intracranial hemorrhage, infection, psychiatric events, change in seizures, and status epilepticus. Adverse events in these categories for all subjects in all RNS® System studies are discussed below.

Serious adverse events related to intracranial hemorrhage (all hemorrhage categories) occurred in 12 of the 256 implanted subjects (4.7%) over the 903 implant years. Hemorrhages were attributed to seizure-related head trauma in 5 of the 12 subjects. Therefore, the percentage of subjects with SAEs related to intracranial hemorrhage that were not attributed to seizure-related trauma was 2.7% (7 subjects) and the event rate was 0.8 events per 100 patient implant years.

Four subjects (1.6%) had an intracranial hemorrhage in the first 28 days and 3 of those were within the first 72 hours after implantation of the Neurostimulator and Leads. These included 2 subjects with epidural hematomas that were evacuated, one subject with a subdural hematoma that required surgical evacuation, and one subject with a small intraventricular hemorrhage identified by CT scan who was observed in the hospital for 1 day.

After the initial month post-implant, there were 8 serious adverse events related to hemorrhage. Two were evacuated, and 1 subject had the Neurostimulator and Leads explanted at the time the subject withdrew from the study (> 13 months after the event). The remaining patients required no surgical intervention.

Nine subjects had no persistent sequelae from the intracranial hemorrhage. Three subjects had sequelae, which included 1 subject with worsening of a pre-existing memory deficit, 1 subject with a persistent right hand paresis and 1 subject who reported an on-going headache.

Serious adverse events related to infections at the implant site occurred in 18 subjects (7.0%) over the 903 implant years. In 2 of the 18 subjects, the implant site infection was attributed to seizure-related head trauma. Therefore, the percentage of subjects with serious non-seizure-related infection was 6.3% and the event rate was 2.0 events per 100 patient implant years.

One infection was diagnosed by a positive culture prior to implantation of the Neurostimulator and Leads; this was believed to be an incompletely treated infection that began with implantation of intracranial electrodes for video-EEG monitoring 3 years before. All infections were treated with antibiotics with or without drainage or debridement. Eleven (4.3%) subjects had the Neurostimulator and/or Leads explanted because of infection. One of the subjects was re-implanted after the infection resolved. There were no infections of the brain, no sepsis and no permanent neurological consequences related to infection.

Many subjects in these studies had a history of depression (49%) and/or suicidality (5.2%). According to responses on the Beck Depression Inventory (BDI-II) during the Baseline Period, 15.6% of subjects had moderate depression before implant and 9.2% endorsed suicidality. Rates of depression and suicidality remained stable post-implant.

In order to fully capture any adverse event that could be representative of suicidality, suicidality was broadly defined to include the MedDRA preferred terms: suicide attempt, suicidal behavior, suicidal ideation, depression suicidal, self-injurious ideation, and suicide. Serious adverse events related to depression and suicidality occurred in 13 subjects, including 2 subjects who committed suicide. 12 of the 13 subjects had a prior history of depression and/or suicidality. Both subjects who committed suicide had a past history of depression; one subject had experienced mild adverse events related to depression during the study.

Neuropsychological testing was performed in order to demonstrate that treatment with the RNS® System had no negative effect on cognitive function. There was no deterioration from baseline in any of the 14 neuropsychological domains tested at the end of the evaluation period or at 1 and 2 years after implant

The most common serious adverse events related to a change in seizures fell in the categories of an increase in seizure frequency (11.3%, 29/256), an exacerbation in seizures (6.6%, 17/256) and a new seizure type (1.2%, 3/256). The majority of these adverse events were considered serious because the subject was admitted for video-EEG monitoring or hospitalized to receive antiepileptic medications. Ninety percent (60/67) of the serious adverse events related to increased seizure frequency or seizure exacerbation resolved (a new type of seizure could not, by definition, resolve). The majority of the 30 subjects with adverse events related to a new type of seizure were because of a milder type of seizure (80%, all mild adverse events). There were only 3 serious adverse events related to a new seizure type and all were because of a change in phenotype.

Eight of the 256 subjects (3.1%) had a serious adverse event related to status epilepticus while implanted. 6 episodes were convulsive and 10 were non-convulsive. 7 subjects had 1 episode each and 1 subject had 9 episodes. Three of these events were considered device-related. One additional subject had convulsive status epilepticus after the RNS® System was explanted but before the subject had withdrawn from the study; the status occurred when the patient had AEDs tapered during an invasive monitoring procedure.

1.9.3.3 Deaths and SUDEP Analysis (Combined RNS® System Studies)

There were eleven deaths in the RNS® System trials. One occurred in the Feasibility investigation, 6 during the Pivotal investigation and 4 in the Long-

term Treatment investigation. Two of the deaths were suicide (1 each in the Pivotal and LTT studies) and were discussed above. Seven were attributed to possible, probable, or definite SUDEP. Five of the deaths due to SUDEP occurred while responsive stimulation was enabled; therefore, the rate of SUDEP for subjects in the RNS® System trials is 4.5 per 1000 patient years of stimulation, which is consistent with the background SUDEP rate for this subject population of 9.3 per 1000 patient years as estimated from the literature.

1.9.3.4 Device Failures and Replacements

Serious adverse events requiring replacement of the Neurostimulator and/or Leads included premature battery malfunction, presumed neurostimulator malfunction, lead damage, and lead revisions.

During the RNS® System studies, 11 subjects (4.3%) had a Neurostimulator replaced due to premature battery depletion. All of these batteries were acquired from a single manufacturer. Since July 2006 batteries have been supplied from other manufacturers, and there have been no malfunctions in batteries from subsequent manufacturers.

Two subjects had their Neurostimulator replaced due to presumed malfunction. One required a Neurostimulator replacement after being assaulted and struck with a board on the head at the site of the Neurostimulator. After the assault, the subject was unable to interrogate the Neurostimulator, however post-implant investigation showed normal Neurostimulator function. Another subject had a replacement because of concern that the battery had depleted early; a post-implant investigation determined that the battery was functioning as expected.

Eight subjects (3.1%) had procedures to revise damaged Leads. Six subjects had Lead fractures in depth Leads placed in the hippocampus; the fracture appeared to be near the burr hole. A single patient had a titanium plate covering a prior craniectomy and required 2 separate procedures to replace Leads that appeared to be cut between the skull and the titanium plate. Another subject had a cortical strip Lead cut during a routine Neurostimulator replacement.

Seven subjects (2.7%) had procedures to revise Leads; these included adjustment of Lead location, change in Leads connected to the Neurostimulator or implant of new Leads. One subject experienced discomfort with stimulation due to the Lead location, therefore the depth Lead was explanted and a new Lead implanted. Six subjects underwent Lead revisions to change the sensing or stimulation location. Two of these subjects had a modification in the position of a Lead in order to improve placement; the Lead was not replaced. Two additional subjects had the Leads connected to the Neurostimulator changed with other Leads that were already implanted. For the last 2 subjects, the investigator replaced Leads that were not optimally located.

1.10 Conclusions Drawn from the Studies

1.10.1 Effectiveness

The RNS® System Pivotal Investigation has demonstrated that responsive stimulation as delivered by the RNS® System reduces the frequency of disabling seizures in a population of persons with medically intractable partial seizures arising from 1 or 2 foci. Significant reductions in seizures were achieved in a group receiving responsive stimulation (Treatment group) compared to a group receiving no stimulation (Sham group). As estimated using the generalized estimating equation model (GEE model), over the entire Blinded Evaluation Period, the Treatment group experienced a reduction in seizure frequency of 37.9% compared to a 17.3% reduction in the Sham group; this difference is statistically significant ($p = 0.012$). By the third month of the Blinded Evaluation Period, the Treatment group experienced a 41.5% reduction in seizure frequency compared to only a 9.4% reduction in the Sham group ($p = 0.008$).

Effectiveness was not only sustained but improved over time, as demonstrated by continued reductions in seizure frequencies over the duration of follow-up. As of the data cutoff date, over 80% of all subjects in the Open Label Period experienced some reduction in seizure frequency. For those subjects who have reached 2 years post-implant, 55% of the subjects experienced a 50% or greater reduction in seizures.

In addition, significant improvements in quality of life were demonstrated at one and two years after treatment with the RNS® System compared to baseline, including improvements in domains strongly associated with better quality of life, such as memory, language, attention and concentration, health discouragement and seizure worry. In the Pivotal study, 40% or more of subjects had clinically significant improvements in total quality of life, and in memory, attention/concentration, health discouragement, and seizure worry.

1.10.2 Safety

Safety was demonstrated in the Feasibility and Pivotal studies in a comparison with historical controls that included procedures related to epilepsy surgery (implantation of intracranial electrodes for purposes of localizing the seizure focus and the epilepsy surgery procedure) and implantation of deep brain stimulation (DBS) systems for treatment of movement disorders. During the evaluation periods, there was no difference between the Treatment and Sham groups in the overall percentage of subjects experiencing a serious adverse event, or any specific type of serious adverse event, demonstrating that there is not an adverse effect of stimulation. In the Feasibility, Pivotal and Long-Treatment studies, adverse events did not increase in frequency or type over time, demonstrating the long term safety of stimulation.

Over the entire RNS® Studies experience with over 903 patient years of implant experience and over 819 patient years of stimulation experience, there were no serious unanticipated device-related adverse events. The device-related serious adverse events reported with the greatest frequency were implant site

infection (5.9%), premature battery depletion (4.3%), increased tonic-clonic seizures (3.9%), medical device removal (3.5%), and increased complex partial seizures (3.1%). The percentage of subjects with serious non-seizure-related intracranial hemorrhage was 2.7%. Implant site infections that were considered serious affected 5.9% of subjects (3.1% requiring explant). The percentage of subjects experiencing adverse events and the specific type of adverse events were consistent with anticipated risks of the comparator procedures or with events anticipated in persons with epilepsy.

Persons with such severe epilepsy are at risk for cognitive deterioration, especially in memory function. However, subjects in the RNS® System Pivotal study and in the Feasibility study had no deterioration in any aspect of neuropsychological function compared to baseline.

1.10.3 Risk Benefit Analysis

The clinical experience from the RNS® System Clinical Investigations demonstrates that the benefits of seizure reduction outweigh the risks of device-related adverse events. The Pivotal study data showed that treatment of medically intractable partial onset epilepsy with responsive stimulation as provided by the RNS® System reduces the frequency of disabling seizures and improves quality of life. The rates of device-related adverse events are acceptably low and there is no adverse effect on mood or neuropsychological function. An analysis of safety data combined from the Feasibility, Pivotal and Long-term Treatment clinical investigations and a review of the related published literature suggests that the safety of the RNS® System is at least equivalent to comparable procedures: implantation of intracranial electrodes for localization of the seizure focus, epilepsy surgery and DBS for movement disorders. Therefore, the NeuroPace® RNS® System has demonstrated safety and effectiveness as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

1.11 Panel Recommendations

(To be completed by FDA.)

1.12 CDRH Decision

(To be completed by FDA.)

1.13 Approval Specifications

(To be completed by FDA.)